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(54) **(S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofuryl-carbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide for treating gastrointestinal motility disorders**

(S)-4-Amino-5-Chloro-2-Methoxy-N-[1-[1-(2-Tetrahydrofuryl-Carbonyl)-4-Piperidinylmethyl]-4-Piperidinyl]benzamid zur Behandlung von Magen-Darmbewegungskrankheiten

(S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofuryl-carbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide pour le traitement des troubles de la motilité gastrointestinale

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- **PATENT ABSTRACTS OF JAPAN vol. 2000, no. 06, 22 September 2000 (2000-09-22) -& JP 2000 080081 A (DAINIPPON PHARMACEUT CO LTD), 21 March 2000 (2000-03-21) -& EP 1 076 055 A (DAINIPPON PHARMACEUTICAL CO) 14 February 2001 (2001-02-14)**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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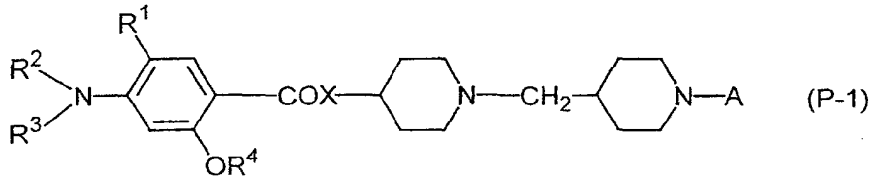
Description

[0001] The present invention relates to an (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide exhibiting a potent gastrointestinal motility enhancing effect based on its agonistic activity on serotonin 4 receptor (hereinafter, occasionally referred to as 5-HT_4 receptor) and having few effects on the heart. This compound is an amide compound of 4-amino-5-chloro-2-methoxybenzoic acid.

[0002] The present invention also relates to a process for the preparation of the compound, a pharmaceutical composition containing it , and an intermediate therefor.

[0003] JP-A-2000-80081 discloses that 1-(1-substituted-4-piperidinylmethyl)-4-piperidinylbenzamide and an ester derivative thereof of the following formula (P-1), which is formed by binding a 1-(1-substituted-4-piperidinylmethyl)-4-amino(or hydroxy)-piperidine derivative with a 4-amino-5-halogeno-2-alkoxybenzoic acid via an amide or ester bond, have selective agonistic effects on 5-HT_4 receptor, and are useful as medicaments in the prophylaxis or treatment of various gastrointestinal diseases, etc.



(P-1)

wherein R^1 is a halogen atom;
R^2 is a hydrogen atom or a lower alkyl group;
R^3 is a hydrogen atom, a lower alkyl group, etc.;
R^4 is a hydrogen atom or a lower alkyl group;
X is -NH- or -O-;
A is a group of the following formula (A-1), (A-2) or (A-3):

$$-(CH_2)_p-C(R^7)(R^8)-COR^9 \quad \text{(A-1)}$$

(in which p is 0, 1, 2, 3, 4 or 5,
R^7 is a hydrogen atom, a lower alkyl group, etc.,
R^8 is a hydrogen atom or a lower alkyl group,
R^9 is a lower alkoxy group, etc.),

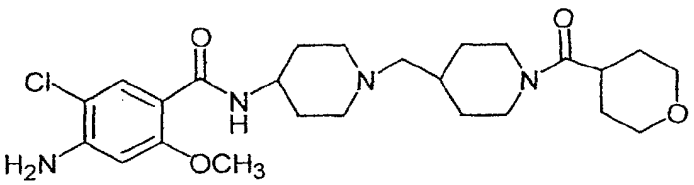
$$-CO-R^{10} \quad \text{(A-2)}$$

(in which R^{10} is a substituted or unsubstituted phenyl-lower alkyl group, a substituted or unsubstituted heteroaryl group, a saturated monocyclic or bicyclic hetero ring, a cycloalkyl group, a lower alkenyl group, a trifluoromethyl group, a lower alkyl group being substituted by a heteroaryl group, etc.),

$$-(CH_2)_q-Z-R^{11} \quad \text{(A-3)}$$

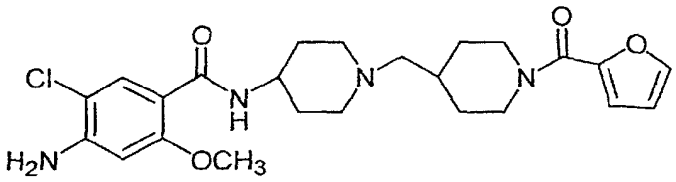
(in which q is 0, 1, 2, 3 or 4,
Z is $-CH_2-$ or -O-,
R^{11} is a hydrogen atom, a lower alkyl group, a cycloalkyl group, etc., provided that when q is 0, then Z is $-CH_2-$, etc.).

[0004] The above publication also discloses, in Example 5 thereof, a compound of the following formula (Compound A) as a compound of the formula (P-1) wherein R^{10} in the above formula (A-2) is a saturated monocyclic hetero ring containing an oxygen atom.



Compound A

[0005] In addition, the above publication discloses, in Example 19 thereof, a compound of the following formula (Compound B) as a compound of the formula (P-1) wherein R^{10} in the formula (A-2) is a heteroaryl group containing an oxygen atom.



Compound B

[0006] However, the above patent publication does not disclose specifically a compound of the present invention of the formula (I) as disclosed below in the form of an (S)-optical isomer, which corresponds to a compound of the formula (P-1) wherein R^{10} in the above formula (A-2) is a 2-tetrahydrofuryl group.

[0007] In the 1990s, 5-HT_4 receptor was found during studies on 5-HT receptor subtypes participating in gastrointestinal motility enhancing effect by metoclopramide and cisapride, and it was confirmed that such benzamide derivatives enhance the gastrointestinal motility by activating 5-HT_4 receptor, this being widely distributed throughout the gastrointestinal organs (cf., J. Pharmacol. Exp. Ther., 252, 1378-1386 (1990); J. Pharmacol. Exp. Ther., 257, 781-787 (1991)). Thus, a compound activating 5-HT_4 receptor may be expected to enhance the gastrointestinal motility, but metoclopramide as mentioned above causes a central nervous system depression based on the antagonistic activity on dopamine D_2 receptor, and cisapride was observed to show disadvantageous effects on the heart, and hence, it is difficult to use these medicaments in the clinical field [cf., J. Pharmacol. Exp. Ther., 282, 220-227 (1997); The Journal of Pediatrics, Jan. 164 (1997)].

[0008] Besides, recently, there has been, as a growing tendency, an increase in the number of patients suffering from symptoms associated with gastrointestinal motility disorders due to today's complicated society and aging society, and under these circumstances, it has been strongly desired to develop an excellent gastrointestinal motility enhancer (gastrointestinal prokinetic agent) with less adverse effects.

[0009] Under these circumstances, we have conducted intensive studies on 1-(1-substituted-4-piperidinylmethyl)-4-piperidine derivatives activating 5-HT_4 receptor, and have found that 1-(1-substituted-4-piperidinylmethyl)-4-piperidinylamide (of the above formula P-1) or a corresponding ester derivative thereof, which is bound with a 4-amino-5-halogeno-2-alkoxybenzoic acid or a 4-amino-5-halogeno-2,3-dihydrobenzo[b]furan-7-carboxylic acid respectively via an amide or ester bond, shows a potent agonistic activity on 5-HT_4 receptor, and is useful as an excellent gastrointestinal motility enhancer (JP-A-2000-80081, supra).

[0010] Although it is apparent that medicaments belonging to this kind of category exhibit sufficient gastrointestinal motility enhancing activity, nevertheless it has strongly been desired to develop medicaments having no disadvantageous effects on the heart, particularly, no action of prolonging the QT interval of an electrocardiogram, which is a serious clinical problem presented by the gastrointestinal motility enhancer cisapride as mentioned above, and having no central nervous system depression based on the dopamine D_2 receptor antagonistic activity as observed with metoclopramide, and it has become important to solve these problems.

[0011] Under these circumstances, in order to find a safer benzoic acid derivative, which exhibits an excellent enhancing activity on the digestive tract with few effects on the heart, etc. as few as possible, or even no, antagonistic effects on dopamine D_2 receptor, we synthesized various derivatives and studied the pharmacological activities thereof.

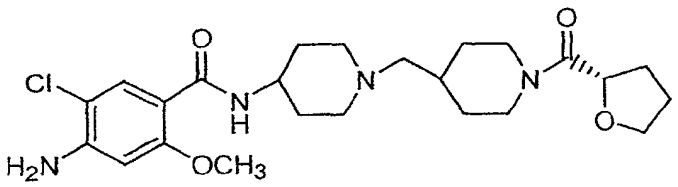
[0012] Aiming at the compounds of the formula (P-1) wherein a saturated monocyclic hetero ring bonds to the carbonyl group as a substituent A, we have tried to convert the substituents into various ones wherein a hetero atom does not directly bond to the carbonyl group, they have finally found that only a compound of the formula (P-1) wherein the substituent A is a specific substituent binding to the carbonyl group at the 2-position of the tetrahydrofuran ring, i.e., 4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide, maintains a potent agonistic activity on 5-HT_4 receptor and a potent inducing activity of defecation by oral administration

thereof, and further that such a compound has high safety with extremely weak effects on the heart.

[0013] 4-Amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide thus newly found has an asymmetric carbon atom at the 2-position of the tetrahydrofuryl ring. Then, we separated the compound into an (S)-isomer and an (R)-isomer, and tried various pharmacological tests thereon. As a result, we have found that these optical isomers showed pharmacological activities such as a 5-HT_4 receptor agonistic activity and an inducing activity of defecation almost equal to the racemic compound thereof, and further that these optical isomers showed few effects on the heart. In addition, we tested these optical isomers with respect to their binding activities to various receptors, and have unexpectedly found that only one of these optional isomers, (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide, is a selective 5-HT_4 receptor agonist having no inhibitory activity of dopamine D_2, which can be a cause for side effects on the central nervous system, and finally have accomplished the present invention.

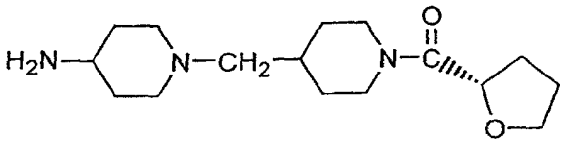
[0014] The present invention addresses the problem of providing a novel4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide exhibiting a potent agonistic activity on 5-HT_4 receptor. The present invention also addresses the problem of providing a compound useful as a gastrointestinal motility enhancer or a gastrointestinal prokinetic agent. A further problem addressed by the present invention is to provide a pharmaceutical composition containing the compound, while a still further problem addressed by the present invention is to provide an intermediate for preparing the compound.

[0015] The present invention provides a 4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]-benzamide of the following formula (I), a pharmaceutically acceptable acid addition salt thereof, and a hydrate thereof,



(I)

and a pharmaceutical composition containing the same, and as an intermediate for preparing the above compound (I), a 4-amino-1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]piperidine of the following formula (V), and an acid addition salt thereof



(V)

[0016] The pharmaceutically acceptable acid addition salt of the compound of the formula (I) includes a salt with an inorganic acid such as a hydrochloride, hydrobromide, hydroiodide, sulfate or phosphate, or a salt with an organic acid such as an oxalate, maleate, fumarate, lactate, malate, citrate, tartrate, benzoate, methanesulfonate or succinate.

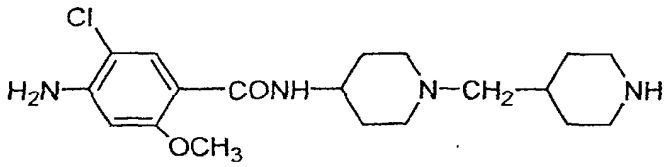
[0017] The acid addition salt of the compound of the formula (V) may be any of the pharmaceutically acceptable acid addition salts as mentioned above, but may be any other acid addition salt which can be formed with the compound (V).

[0018] The compound of the formula (I) and a pharmaceutically acceptable acid addition salt thereof, and the compound of the formula (V) and an acid addition salt thereof may exist in the form of a hydrate or a solvate, and the present invention also includes these hydrates and/or solvates as well.

[0019] A compound of the present invention may be prepared, for example, by the following processes.

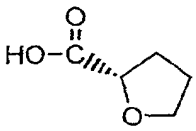
Process (a)

[0020] A compound of the formula (I) may be prepared by reacting a compound of the formula (II):



(II)

with a compound of the following formula (III):



(III)

(Chemical name: (S)-tetrahydrofuran-2-carboxylic acid) or a reactive derivative thereof.

[0021] The reactive derivative of the compound (III) includes, for example, a lower alkyl ester (especially, a methyl ester), an active ester, an acid anhydride, and an acid halide (especially, an acid chloride). The active ester includes, for example, p-nitrophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-hydroxysuccinimide ester, N-hydroxyphthalimide ester, 1-hydroxybenzotriazole ester, 8-hydroxyquinoline ester, and 2-hydroxyphenyl ester. The acid anhydride includes, for example, a symmetric acid anhydride and a mixed acid anhydride. The mixed acid anhydride includes, for example, a mixed acid anhydride with an alkyl chlorocarbonate such as ethyl chlorocarbonate and isobutyl chlorocarbonate, a mixed acid anhydride with an aralkyl chlorocarbonate such as benzyl chlorocarbonate, a mixed acid anhydride with an aryl chlorocarbonate such as phenyl chlorocarbonate, and a mixed acid anhydride with an alkanoic acid such as isovaleric acid and pivalic acid.

[0022] When the compound (III) per se is used, the reaction can be carried out in the presence of a condensing agent such as 1,3-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, N,N'-carbonyldiimidazole, benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate, N,N'-disuccinimidyl carbonate, 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, diphenylphosphoryl azide, and propanephosphonic anhydride. When 1,3-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride is used as a condensing agent, N-hydroxysuccinimide, 1-hydroxybenzotriazole, 3-hydroxy-1,2,3-benzotriazin-4(3H)-one, or N-hydroxy-5-norbornen-2,3-dicarboximide, etc. may be added into the reaction system.

[0023] The reaction of the compound (III) or a reactive derivative thereof with the compound (II) is carried out in a solvent or without a solvent. The solvent should be selected according to the kinds of the reactive derivative of compound (III), etc., and includes, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene) , ethers (e.g., diethyl ether, tetrahydrofuran, dioxane) , halogenated hydrocarbons (e.g., methylene chloride, chloroform) , ketones (e.g., acetone, methyl ethyl ketone), ethyl acetate, acetonitrile, dimethylformamide, dimethyl sulfoxide, 1-methyl-2-pyrrolidone, and these solvents are used alone or in a mixture of two or more solvents.

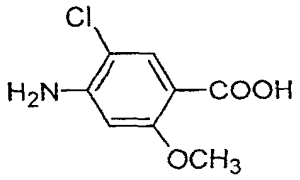
[0024] The reaction may optionally be carried out in the presence of a base, if necessary. The base includes, for example, an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide), an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate), and organic bases (e.g., triethylamine, tributylamine, diisopropylethylamine, N-methylmorpholine), but an excess amount of the compound (II) may be used instead of a base.

[0025] The reaction temperature varies according to the kinds of the reactive derivative of compound (III), etc. to be used, but it is usually in the range of about -30°C to about 250°C, preferably in the range of about -10°C to about 150°C.

[0026] The compound of the formula (II) may be prepared by the method disclosed in JP-A-2000-80081, and the compound of the formula (III), i.e., (S)-tetrahydrofuran-2-carboxylic acid, is commercially available or may be prepared by a conventional method.

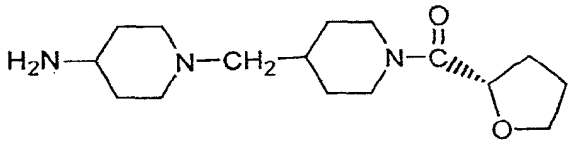
Process (b)

[0027] The compound of the formula (I) may be prepared by reacting a compound of the formula (IV):



(IV)

or a reactive derivative thereof with a compound of the following formula (V):



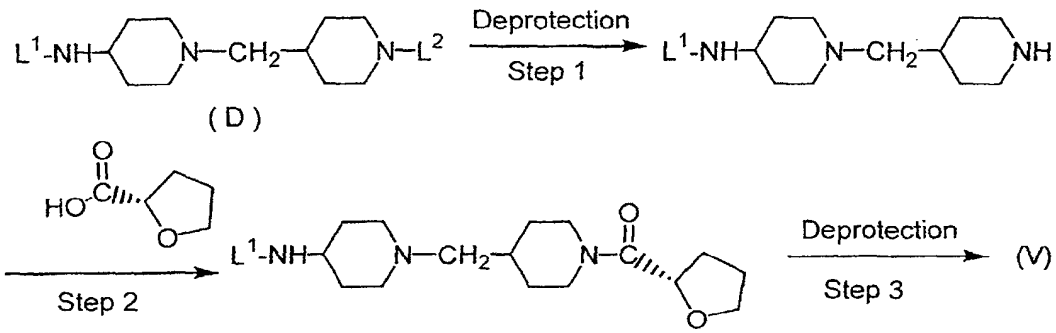
(V)

[0028] The reaction of the compound (IV) or a reactive derivative thereof with the compound (V) is carried out in a solvent or without a solvent.

[0029] The reactive derivative of the compound (IV) may be the same type of derivative, i.e. lower alkyl esters, active esters, acid anhydrides, and acid halides, as described in the above Process (a). When the compound (IV) per se is used, the reaction can be carried out in the presence of the same condensing agent as disclosed in the above Process (a). The solvent to be used may be the same as any of those disclosed in the above Process (a), and should be selected according to the kinds of the reactive derivative of compound (IV), etc. to be used. The reaction is carried out in the presence of a base, if necessary. The base may be the same as any of those disclosed in the above Process (a), but an excess amount of the compound (V) may be used instead of a base. The reaction temperature varies according to the kinds of the reactive derivative of compound (IV) to be used, but it is usually in the range of about -30°C to about 250°C, preferably in the range of about -10°C to about 150°C.

[0030] The compound of the formula (V) may be prepared by the method disclosed in the following Chart 1.

Chart 1



wherein L^1 and L^2 are protecting groups.

[0031] Step 2 in the above Chart 1 is carried out in the same manner as in the above Process (a), and Step 1 and Step 3 therein are carried out in the same manner as in the process for the removal of a protecting group as described below.

REMOVAL OF PROTECTING GROUP:

[0032] In Chart 1, the protecting groups represented by L^1 and L^2 may be any protecting groups capable of removal by hydrolysis or hydrogenolysis. The protecting group capable of removal by hydrolysis includes, for example, ethoxycarbonyl group, t-butoxycarbonyl group, acetyl group, benzoyl group, trifluoroacetyl group, benzyloxycarbonyl group, 3- or 4-chlorobenzyloxycarbonyl group, triphenylmethyl group, methanesulfonyl group, or p-toluenesulfonyl group, and

the protecting group capable of removal by hydrogenolysis includes, for example, benzyloxycarbonyl group, 3- or 4-chlorobenzyloxycarbonyl group, or benzylsulfonyl group.

[0033] The deprotection by hydrolysis may be carried out by a conventional method, for example, in a suitable solvent under water-soluble inorganic or organic acidic or basic aqueous conditions, or under organic acidic conditions in a suitable solvent. The solvent includes, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene), ethers (e.g., diethyl ether, tetrahydrofuran, dioxane), halogenated hydrocarbons (e.g., methylene chloride, chloroform) , ketones (e.g., acetone, methyl ethyl ketone) , alcohols (e.g., methanol, ethanol, isopropanol), ethyl acetate, acetonitrile, water, and a mixture of these solvents. The acid includes, for example, inorganic acids (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid), and organic acids (e.g., formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid) . The base includes, for example, an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide), and an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate). The reaction is usually carried out at a temperature of from about 0°C to about 150°C.

[0034] The deprotection by hydrogenolysis may be carried out by a conventional method, for example, by reacting in the presence of a catalyst (e.g., palladium-on-carbon, Raney-nickel), and hydrogen gas or a hydrogen donor (e.g., ammonium formate, cyclohexane) in a suitable solvent. The solvent includes, for example, alcohols (e.g., ethanol, methanol), water, acetic acid, dioxane, tetrahydrofuran, ethyl acetate, and dimethylformamide. The reaction is usually carried out at a temperature of from about 0°C to about 80°C, under atmospheric pressure or under pressure.

[0035] When L^1 and L^2 capable of removal by hydrolysis are used as protecting groups, they should be selected from those capable of removal under different conditions.

[0036] The desired compound obtained in the above Processes can be isolated and purified by a conventional method such as chromatography, recrystallization or re-precipitation.

[0037] The compound (I) can be obtained either in the form of a free base or in the form of an acid addition salt thereof, according to the kinds of reaction conditions. The acid addition salt can be converted into a free base by a conventional method, for example, by treating it with a base such as alkali metal carbonate or an alkali metal hydroxide. On the other hand, the compound (I) in the form of a free base can be converted into an acid addition salt thereof by treating it with various acids in a conventional manner.

[0038] The test results on the pharmacological activities of the present compound are as follows.

Test Compounds:

[0039]

(1) Present compound

Compound 2 (Compound of Example 2): (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide fumarate

(2) Reference Compound

Compound R (Compound of Reference Example 2): (R)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide - fumarate (an enantiomer of Compound 2)

Compound A: 4-amino-5-chloro-2-methoxy-N-[1-[1-(4-tetrahydropyranylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide · fumarate · 1/4 hydrate (Compound of Example 5 of JP-A-2000-80081), M.p. 235-237°C (recrystallized from ethanol)

Compound B: 4-amino-5-chloro-N-[1-[1-(2-furoyl)-4-piperidinylmethyl]-4-piperidinyl]-2-methoxybenzamide - fumarate - 1/2 hydrate (Compound of Example 19 of JP-A-2000-80081), M.p. 179-181°C (recrystallized from ethanol)

Compound C (Compound of Reference Example 3): 4-amino-5-chloro-2-methoxy-N-[1-1-(3-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide . fumarate (a racemic compound wherein the substitution position of tetrahydrofuran is different from the present compound)

(3) Gastrointestinal motility enhancer or gastrointestinal prokinetic agent:

Cisapride: [Chemical name: cis-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide; cf., Merck Index, 12 ed., 2377 (1996)]

Metoclopramide: [Chemical name: 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide; cf., Merck Index, 12 ed., 6226 (1996)]

Experiment 1: Serotonin 4 (5-HT_4) receptor binding assay

[0040] 5-HT_4 receptor binding assay and the preparation of 5-HT_4 receptor membrane fractions therefor were carried out according to a modified method of the method of Grossman et al., British J. Pharmacol., 109, 618-624 (1993).

[0041] Std-Hartley guinea pigs weighing 300-400 g were decapitated, and the brain thereof was immediately taken out, and the striatum was dissected. To the tissue thus obtained was added 15-times volume of Hepes buffer (50 mM, pH7.4, 4°C), and the mixture was homogenized in a Teflon homogenizer, and centrifuged at 48,000 x g at 4°C for 15 minutes. The pellet thus obtained was suspended in the same Hepes buffer in a volume of 1 ml per 30 mg of the wet tissues to give receptor membrane fractions.

[0042] In assay tubes, the Hepes buffer (50 mM. pH 7.4, 4°C, 1 ml) containing 0.1 nM [^{3}H]-GR113808 (GR113808: [1-[2-(methylsulfonylamino)ethyl]-4-piperidinyl]methyl 1-methylindole-3-carboxylate), the receptor membrane fraction, and either test compound or 30 μM serotonin was incubated at 37°C for 30 minutes. The reaction was terminated by rapid vacuum filtration and washing with ice-cold 50 mM Tris-HCl buffer (pH 7.7, 3 X 4 ml) through Whatman GF/B filter paper using a Brandel cell harvester. Prior to the filtration, the filter to be used was presoaked in a 0.1 % solution of polyethylenimine for one hour. The radioactivity on the filter was determined with ACS-II scintillation cocktail by a liquid scintillation counter.

[0043] The concentration of the test compounds causing 50 % inhibition of specific binding of the [^{3}H]-GR113808 (IC_{50} value) was determined by inhibitory rate of the test compound against the specific binding which was obtained by subtracting the non-specific binding from the total [^{3}H]-GR113808 binding. The results are shown in Table 1.

Table 1:

Serotonin 4 (5-HT_4) receptor binding activity	
Test Comp.	IC_{50} (nM)
Compound 2*	13.5
Cisapride	23.0

*: The compound of Example 2

[0044] As is shown in Table 1, the IC_{50} value of the present compound indicated that the present compound shows a more potent affinity for 5-HT_4 receptor than cisapride.

Experiment 2: Dopamine D_2 receptor binding assay

[0045] Dopamine D_2 receptor binding assay and the preparation of receptor membrane fractions therefor were carried out according to a modified method of the method of Creese, I. et al., Eur. J. Pharmacol., 46, 337 (1977) and Peroutka, S.J. and Hamik, A., Eur. J. Pharmacol., 148, 297 (1988).

[0046] Crude synaptosome membrane fractions from rat brain was used as a receptor membrane fraction, and [^{3}H] spiperone (D_2) was used as a labelled ligand. A buffer (final volume: 1 ml) containing a receptor membrane fraction and a labelled ligand therefor was incubated for a prescribed period in the presence of a test compound in various concentrations, and the radioactive ligand binding to the receptor was separated on the filter paper using a cell harvester (manufactured by Brandel). The radioactivity on the filter was determined by a liquid scintillation counter, and the total binding of the ligand to the receptor was determined. On the other hand, the non-specific binding was determined in the presence of an excess amount of non-labelled ligand (spiperone (D_2)), and the specific binding was obtained by subtracting the non-specific binding from the total binding. The concentration of the test compound causing 50 % inhibition of specific binding of the labelled ligand (IC_{50} value) was determined by probit method. The results are shown in Table 2.

Table 2:

Dopamine D_2 receptor binding activity	
Test Comp.	IC_{50} (nM)
Compound 2*	> 10000
Compound R	948
Metoclopramide	480

*: The compound of Example 2

Table 2: (continued)

Dopamine D_2 receptor binding activity	
Test Comp.	IC_{50} (nM)
Cisapride	390

[0047] In the dopamine D_2 receptor binding assay, the IC_{50} value of the present compound is more than 10000 nM, which means that the present compound hardly shows affinity for dopamine D_2 receptor. On the other hand, the IC_{50} value of the (R) optical isomer (Compound R), which is an enantiomer of Compound 2, is 948 nM, which means that Compound R shows an affinity for dopamine D_2 receptor although it is somewhat weaker than those of metoclopramide and cisapride.

Experiment 3: Assay on defecation in mice

[0048] Male mice of Std-ddY strain weighing 25-30 g were used. Free access to food and water was allowed up to the beginning of the procedure.

[0049] The mice (each group: five mice) were placed in a mesh bottom cage for fasting, and they were allowed a period for acclimatisation to the new environment of about one hour prior to the start of the experiment. A test compound, which was previously suspended in a 0.5 % tragacanth solution, was administered orally to the mice. The fecal pellets were collected at 30, 60 and 120 minutes after the treatment of a test compound, and weighed.

[0050] The statistical judgment of efficacy was carried out between the control group (treated with a 0.5 % tragacanth solution) and the test compound-treated group, and determined by Dunnett's test. The results are shown in Table 3.

-: Inactive
+: Moderately stimulated ($P<0.05$)
+ +: Markedly stimulated ($p<0.01$)

Table 3

Assay on defecation in mice		
Test Comp.	Dosage (mg/kg)	Effect
Compound 2*	1.0	++
	3.0	++
Compound R	1.0	++
	3.0	++
Compound A	1.0	-
	3.0	-
	10	++
Compound B	1.0	+
	3.0	+
	10	++
Compound C	1.0	+
	3.0	++
Cisapride	3.0	-
	30	-

*: The compound of Example 2

[0051] As is shown in Table 3, the present compound (Compound 2) showed a potent enhancing activity of defecation at a dose of either 1 mg/kg or 3.0 mg/kg. On the other hand, the compound of Example 5 of JP-A-2000-80081 (Compound A) showed no effects on defecation at both doses of 1.0 mg/kg and 3.0 mg/kg, and the compound of Example

19 of that publication (Compound B) showed an enhancing effect of defecation, but the effect thereof was weaker than that of Compound 2. Although Compound C (racemic compound), which is different from the present compound in the substitution position of the tetrahydrofuran ring, showed an enhancing effect on defecation at a dose of 3.0 mg/kg, it was not as strong as that of the present compound. In addition, cisapride did not show any enhancing effects on defecation at 3.0 mg/kg, and even at a high dose of 30 mg/kg.

Experiment 4: Gastrointestinal motility activity in conscious dog

[0052] Male beagle dogs were anesthetized with pentobarbital, and the abdominal cavity was opened, and force transducers (F-121S; manufactured by Star Medical Inc.) were sutured onto the seromuscular layer of the colon to make it possible to measure circular muscle contractions. Three or four force transducer were sutured onto in the colon from the lower part to the upper part at regular intervals. The lead wires from the transducers were brought out outside the body through a skin incision made between the scapulae, and were protected in a package of a jacket protector. The gastrointestinal motility activity was measured 2 or 3 weeks after the operation. The lead wires from the force transducers were connected with a telemeter system (DAS-800T: manufactured by Star Medical Inc.), and the gastrointestinal motility activity was analyzed by a personal computer system connected therewith and recorded. A test compound was suspended in a 0.5 % tragacanth solution, and administered via a cannula to be placed in the stomach to the dogs, after one hour or more from feeding. The measurement was continued for 2 hours after the administration of test compounds.

[0053] The number of dogs showing Giant Migrating Contraction (GMC) and defecation within 2 hours after the administration of a test compound is indicated in Table 4.

Table 4

Gastrointestinal motility activity in dogs			
Test compound	Dosage (mg/kg)	Number to dogs which showed GMC*3/total number of dogs to be tested	Number of dogs which showed defecation/ total number of dogs to be tested
Control*2		0/5	0/5
Compound 2*1	0.3	1/4	1/4
	0.1	3/5	2/5
	0.3	4/5	3/5
Cisapride	10	1/7	1/7

*1: The compound of Example 2

*2: Control: 0.5 % Tragacanth solution was administered.

*3: GMC (Giant Migrating Contraction): Giant contraction wave migrating from the upper part of the colon to the lower part of the colon

[0054] As is shown in Table 4, the present compound induced GMC at low doses of 0.1 mg/kg and 0.3 mg/kg in the gastrointestinal motility test on the dogs, and an enhancing effect of defecation was also observed. On the other hand, cisapride hardly shows effects of enhancing of defecation even at a high dose of 10 mg/kg.

Experiment 5: Effect on electrocardiogram in guinea pigs (QTc: QT interval corrected for heart rate)

[0055] Male guinea pigs of Std-Hartley strain weighing 350-500 g were anesthetized with urethan (1.5 g/kg, ip). Under artificial respiration, a test compound was continuously infused intravenously to the guinea pigs for 15 minutes at a flow rate of 0.2 ml/kg/min., and the maximum dose was set at 30 mg/kg, and the QTc was calculated from the electrocardiogram by the following equation.

$$QTc = QT(\text{second}) \Big/ \sqrt{RR(\text{second})}$$

QT (second): time from the beginning of Q-wave to the end of T-wave in electrocardiogram (usually, expressed by

"second") [Expert Nurse, Vol. 3, No. 13, extra number of November, p. 19 (1987)]
RR (second): time from the peak of R-wave to the peak of the next R-wave in electrocardiogram (usually, expressed by "second").

[0056] The analysis of the electrocardiogram QTc was carried out by using Fluclet® 3.0 (manufactured by Dainippon Pharmaceutical Co., Ltd.), and the dose to be required to prolong the QTc intervals by 5 % ($ED_{5\%}$) was calculated. The results are shown in Table 5.

Table 5

Effect on electrocardiogram in guinea pigs (QTc)	
Test compound	$ED_{5\%}$, iv (mg/kg)
Compound 2*	24.9
Compound R	17.4
Compound A	16.9
Compound B	3.2
Compound C	9.4
Cisapride	0.3

*: The compound of Example 2

[0057] Among the compounds showing a gastrointestinal motility enhancing activity (gastrointestinal prokinetic activity), certain benzamide-type compounds represented by cisapride have been known to disadvantageously affect the heart. Consequently, as an index for evaluating the effects on the heart, a dose to be required to prolong the QTc intervals by 5 % of the electrocardiogram ($ED_{5\%}$) in guinea pigs was measured, which has widely been used.

[0058] As is shown in Table 5, the $ED_{5\%}$ value of cisapride for the QTc intervals of electrocardiogram in guinea pigs was quite low, i.e. 0.3 mg/kg, and on the other hand, the $ED_{5\%}$ value of the present compound was high, i.e., 24.9 mg/kg, and from these results, the present compound can be considered to show a minimal effect on the heart at a clinical dose.

[0059] On the other hand, the $ED_{5\%}$ value of the compound of Example 5 of JP-A-2000-80081 (Compound A) was comparatively high, i.e., 16.9 mg/kg, but as is shown in Experiment 3 as mentioned above, the gastrointestinal motility enhancing activity of the compound was quite weak, and hence, this compound cannot satisfy the object of the present invention. Furthermore, the $ED_{5\%}$ value of the compound of Example 19 of that publication (Compound B) was low, i.e., 3.2 mg/kg, suggesting that Compound B has serious effects on the heart. In addition, Compound C, being different from the present compound only in the substitution position of the tetrahydrofuran ring, potently prolonged QTc intervals, although being not as strong as Compound B.

Experiment 6: Acute Toxicity

[0060] Male mice of Std-ddY strain weighing 25-30 g were used in a group of 5 or more animals. A test compound was suspended in physiological saline solution or a 1 % lactose solution and administered intravenously to the mice. Then, the lethality of the mice was observed for 7 days after the treatment, and 50 % lethal dose (LD_{50}) was determined. The LD_{50} value of the present compound was more than 200 mg/kg.

[0061] As is shown in the results of the above pharmacological experiments 1 to 6, the present compound only showed the following good results.

(1) The present compound showed a more potent affinity for 5-HT_4 receptor in participating in gastrointestinal motility enhancing activity than cisapride.
(2) The present compound showed a remarkable enhancing activity of defecation in the mice by oral administration at a dose of 1.0 mg/kg.
(3) The present compound induced GMC in more than half of tested animals at a low dose of 0.1 mg/kg and furthermore showed an enhancing activity of defecation in the gastrointestinal motility enhancing activity on dogs.
(4) The present compound showed a sufficiently large $ED_{5\%}$ value in the electrocardiogram test (QTc) in guinea pigs. That is, at a prospective clinical dose, the present compound can be considered to show a minimal effect on the heart.
(5) The present compound showed the IC_{50} value of more than 10000 nM in the dopamine D_2 binding assay, i.e., it showed a quite weak affinity for dopamine D_2 receptor. That is, it can be considered that the present compound

shows no side effects with respect to the dopamine D_2 receptor antagonistic activity.

(6) The present compound can be considered not to have a problem with respect to toxicity because it has an LD_{50} value of more than 200 mg/kg.

[0062] As is explained above, the present compound and a pharmaceutically acceptable acid addition salt thereof show (1) a potent affinity for 5-HT_4 receptor, (2) gastrointestinal motility enhancing effect such as enhancing activity of defecation by oral administration in the animal tests, (3) a quite minimal effect on the heart, and (4) no antagonistic activity on dopamine D_2 receptor, which is a cause of side effects, and hence, the present compound and a pharmaceutically acceptable acid addition salt thereof can be used in the treatment or prophylaxis of gastrointestinal diseases or disorders as a selective 5-HT_4 receptor agonist. Especially, the present compound and a pharmaceutically acceptable acid addition salt thereof show an excellent motility enhancing activity for the lower gastrointestinal tract such as an enhancing activity of defecation, and hence, they can be used in the prophylaxis or treatment of gastrointestinal diseases such as irritable bowel syndrome, flaccid constipation, habitual constipation, drug-induced constipation (e. g., constipation induced by morphine, or a psychotropic), or as a pretreatment of endoscopy or X-ray examination by injection of barium into the colon, or in the treatment or prophylaxis of gastrointestinal diseases such as acute or chronic gastritis, reflux esophagitis, gastric or duodenal ulcer, gastric neurosis, paralytic ileus after surgery, senile ileus, postgastrectomy syndrome and intestinal pseudo-obstruction, as well as in the prophylaxis or treatment of anorexia, nausea, vomiting, abdominal fullness, upper abdominal discomfort, visceral pain, heartburn and eructation which are accompanied by the above mentioned gastrointestinal diseases, and diseases such as gastric or duodenal ulcer, scleroderma, diabetes, biliary duct disorders, etc. Moreover, the present compound and a pharmaceutically acceptable acid addition salt thereof can be used in the treatment or prophylaxis of central nervous diseases (e.g., schizophrenia, depression, memory disturbance, anxiety) or urinary diseases (e.g., urinary disturbances such as dysuria accompanied by urinary obstruction, prostatomegaly). Thus, the present compound and a pharmaceutically acceptable acid addition salt thereof can be used in the treatment or prophylaxis of various diseases, especially gastrointestinal dysfunction accompanied by the above-mentioned diseases, or especially the treatment, etc. of digestive diseases or various diseases as mentioned above, and hence, they are useful as a gastrointestinal motility enhancer (gastrointestinal prokinetic agent).

[0063] Especially, as shown in the above pharmacological experiments, the present compound shows a potent 5-HT_4 receptor agonistic activity and a potent enhancing activity of defecation without showing any antagonistic activity on dopamine D_2 receptor, which may cause side effects, and hence, the present compound shows an excellent usefulness such as quite few side effects on the heart.

[0064] The compound of the present invention can be administered either orally, parenterally or rectally. The dose of the compounds of the present invention varies according to the kinds of the compound, the administration routes, the conditions, ages of the patients, etc., but it is usually in the range of 0.01-5 mg/kg/day, preferably in the range of 0.05-1 mg/kg/day.

[0065] The compound of the present invention and a pharmaceutically acceptable acid addition salt thereof are usually administered in the form of a pharmaceutical preparation, which is prepared by mixing thereof with a pharmaceutically acceptable carrier or diluent. The pharmaceutically acceptable carrier or diluent may be any conventional ones usually used in the pharmaceutical field, and do not react with the compound of the present invention. Suitable examples of the pharmaceutically acceptable carrier or diluent are, for example, lactose, inositol, glucose, mannitol, dextran, sorbitol, cyclodextrin, starch, partly pregelatinized starch, white sugar, magnesium metasilicate aluminate, synthetic aluminum silicate, crystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl starch, calcium carboxylmethyl cellulose, ion exchange resin, methylcellulose, gelatin, gum arabic, pullulan, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, alginic acid, sodium alginate, light anhydrous silicic acid, magnesium stearate, talc, tragacanth, bentonite, veegum, carboxyvinyl polymer, titanium oxide, sorbitan fatty acid ester, sodium laurylsulfate, glycerin, glycerin fatty acid ester, purified lanolin, glycerogelatin, polysorbate, macrogol, vegetable oil, wax, water, propyleneglycol, ethanol, sodium chloride, sodium hydroxide, hydrochloric acid, citric acid, benzyl alcohol, glutamic acid, glycine, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, etc.

[0066] The pharmaceutical preparation is, for example, tablets, capsules, granules, powders, syrups, suspensions, injection preparations, suppositories, nasal drops, patches, sublingual preparations, etc. These preparations may be prepared by a conventional method. In the preparation of liquids, the compound of the present invention may be dissolved or suspended in water or a suitable other solvent, when administered. Tablets and granules may be coated by a conventional method.

[0067] These preparations may contain the compound of the present invention or a pharmaceutically acceptable acid addition salt thereof at a ratio of at least 0.01 % by weight, preferably at a ratio of 0.1-70 % by weight, based on the whole weight of the preparation. These preparations may also contain other therapeutically effective compounds as well.

[0068] Embodiments of the present invention are illustrated in more detail by the following Reference Examples and Examples. The identification of the compounds is carried out by Elemental analysis, Mass spectrum, IR spectrum, NMR spectrum, etc.

Example A

Preparation of 4-amino-1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]piperidine:

[0069]

(1) To a solution of 1-(1-benzyloxycarbonyl-4-piperidinylmethyl)-4-(t-butoxycarbonylamino)piperidine (10.0 g) in ethanol (100 ml) and water (10 ml) is added a 10 % palladium-on-carbon (1.2 g), and the mixture is reduced at a room temperature under at a moderate pressure (3.0 kg/cm^2). After the consumption and disappearance of the starting compound is confirmed (about 2 hours thereafter), the catalyst is removed by filtration. The filtrate is evaporated under reduced pressure to give crude 4-(t-butoxycarbonylamino)-1-(4-piperidinylmethyl)piperidine (about 7 g) as a white solid.

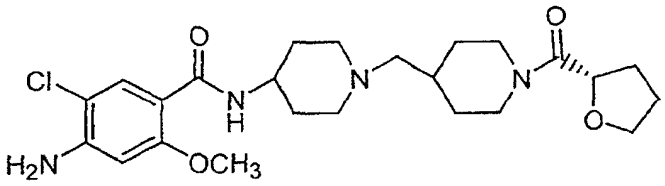
(2) A mixture of the above compound (3.2 g), (S)-tetrahydrofuran-2-carboxylic acid (1.4 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.5 g), and chloroform (100 ml) is stirred at room temperature for 15 hours. The reaction solution is washed successively with a small amount of saturated aqueous sodium hydrogen carbonate solution and a small amount of saturated brine, and dried over anhydrous magnesium sulfate. The solvent is evaporated under reduced pressure, and the resulting oily product is purified by silica gel column chromatography (eluent; ethyl acetate: methanol = 9:1) to give (S)-4-(t-butoxycarbonylamino)-1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]piperidine (2.1g) as a solid.

(3) To a solution of the above product (2.1 g) in methylene chloride (50 ml) is added trifluoroacetic acid (3 ml), and the mixture is stirred at room temperature for 1 hour. The solvent and the excess amount of trifluoroacetic acid are concentrated to dryness under reduced pressure. Toluene is added to the residue, and the solvent is evaporated again under reduced pressure. Chloroform is added to the residue, and thereto is further added a small amount of 30 % aqueous potassium carbonate solution, and the mixture is vigorously stirred at room temperature. The organic layer is separated, and the aqueous layer is extracted twice with chloroform. The organic layers are combined and dried over anhydrous magnesium sulfate. The solvent is evaporated under reduced pressure to give the desired compound (1.6 g) as an oily product.

Example 1

Preparation of (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide (Compound 1):

[0070]



[0071] A mixture of (S)-tetrahydrofuran-2-carboxylic acid (7.4 g), 4-amino-5-chloro-2-methoxy-N-[1-(2-piperidinylmethyl)-4-piperidinyl]-benzamide (20 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (13.1 g), and chloroform (200 ml) is stirred at room temperature overnight. The reaction solution is washed twice with an aqueous sodium hydrogen carbonate solution (50 ml), and dried over anhydrous magnesium sulfate. The solvent is evaporated under reduced pressure, and to the resulting residue is added ethyl acetate (50 ml), and the mixture is stirred at room temperature. The precipitated crystals are collected by filtration under reduced pressure, washed twice with a mixture of ethyl acetate and hexane (1:1, 30 ml), and dried to give the desired compound (Compound 1) (22.6 g).

M. p.: 146-148°C (recrystallized from ethyl acetate)

^{1}H-NMR ($CDCl_3$, δ ppm): 0.98-1.29 (2H, m), 1.44-1.7 (2H, m), 1.7-2.3 (14H, m), 2.59 (1H, m), 2.73 (2H, br-d, J=11.6Hz), 3.01 (1H, m), 3.8-4.1 (5H, m), 3.89 (3H, s), 4.5-4.7 (2H, m), 6.29 (1H, s), 7.62 (1H, d, J=7.5Hz), 8.10 (1H, s)

IR spectrum (ν_{max} cm^{-1}): 3385, 3317, 1639, 1591, 1537

Elemental analysis for $C_{24}H_{35}ClN_4O_4 \cdot 0.25\ H_2O$
Calculated (%): C, 59.62; H, 7.40; N, 11.59; Cl, 7.33
Found (%): C, 59.86; H, 7.19; N,11.51; Cl, 7.31

Example 2

Preparation of (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide · fumarate (Compound 2):

[0072] To (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide (10.0 g) obtained in Example 1 is added ethanol (150 ml), and the mixture is stirred under heating at an outer temperature of about 60°C. To this solution is added fumaric acid (2.42 g), and the mixture is stirred at an outer temperature of about 80°C for 3 hours. The mixture is allowed to cool to room temperature, and the precipitated crystals are collected by filtration under reduced pressure, washed twice with ethanol (30 ml), and dried to give the desired compound (Compound 2) (12.2 g).

M. p.: 232-235°C

[0073] The compound thus obtained shows the retention time of 9.36 minutes in high-performance liquid chromatography (HPLC) under the following conditions, and the optical purity thereof is more than 99 % ee (the retention time of the R-isomer is 11.45 minutes).

HPLC conditions:

[0074] HPLC column: CHIRALPAK AS (manufactured by Daicel Chemical Industries, Ltd.)
Inner diameter: 4.6 mm x 250 mm
Mobile phase: hexane:ethanol:acetonitrile:diethylamine = 70:22:8:0.4
Flow rate: 0.8 ml/min.
Column temperature: 30°C
Wave length for detection: 280 nm
^{1}H-NMR (DMSO-d_6, δ ppm): 0.8-1.15 (2H, m), 1.45-1.7 (2H, m), 1.7-1.9 (6H, m), 1.9-2.1 (2H, m), 2.1-2.35 (4H, m), 2.4-2.6 (2H, m), 2.7-3.1 (3H, m), 3.88 (3H, s), 3.7-3.9 (3H, m), 3.97 (1H, br-d,J=12.5Hz), 4.31 (1H, br-d, J=12.8Hz), 4.63 (1H, t, J=6.5Hz), 5.94 (2H, s, NH_2), 6.48 (1H, s), 6.60 (2H, s), 7.66 (1H, s), 7.73 (1H, d, J=7.5Hz, CONH)
IR spectrum ($\nu_{max}cm^{-1}$): 3373, 1643, 1591, 1545
Elemental analysis for $C_{24}H_{35}ClN_4O_4 \cdot C_4H_4O_4$
Calculated (%): C, 56.51; H, 6.61; N, 9.41; Cl, 5.96
Found (%): C, 56.40; H, 6.50; N,9.39; Cl, 5.96

Example 3

Preparation of (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide · maleate (Compound 3):

[0075] To (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide (25 g) obtained in Example 1 is added ethanol (125 ml), and the mixture is stirred at room temperature. The compound is completely dissolved, and thereto is added maleic acid (6.66 g), and the mixture is stirred under heating at a bath temperature of 100° for 3 hours. The mixture is gradually cooled to room temperature, and the resulting crystals are collected by filtration, and washed twice with ethanol (30 ml). The crystals are dried to give crude crystals containing ethanol (29 g). To the crude crystals (21.4 g) are added ethanol (86 ml) and water (8.6 ml), and the mixture is stirred under heating at a bath temperature of 100°C. After the crystals are completely dissolved, the mixture is gradually allowed to cool to room temperature. The precipitated crystals are collected by filtration, washed twice with ethanol (30 ml), and dried to give the desired compound (Compound 3) (18 g).

M. p.: 232-235°C
Elemental analysis for $C_{24}H_{35}ClN_4O_4 \cdot C_4H_4O_4$
Calculated (%): C, 56.51; H,6.61; N,9.41; Cl, 5.96
Found (%): C, 56.36; H,6.71; N,9.43; Cl, 5.71

Reference Example 1

Preparation of 4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide · fumarate (Compound RS):

[0076] The desired compound (Compound RS) is obtained in a manner similar to that of Example 1 and Example 2 except that tetrahydrofuran-2-carboxylic acid is used instead of (S)-tetrahydrofuran-2-carboxylic acid in Example 1.
M. p.: 229-234°C (recrystallized from ethanol)

Reference Example 2

Preparation of (R)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide · fumarate (Compound R):

[0077] The desired compound (Compound R) is obtained in a manner similar to that of Example 1 and Example 2 except that (R)-tetrahydrofuran-2-carboxylic acid is used instead of (S)-tetrahydrofuran-2-carboxylic acid in Example 1.
M. p.: 228-230°C (recrystallized from ethanol)

Reference Example 3

Preparation of 4-amino-5-chloro-2-methoxy-N-[1-[1-(3-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide (Compound C):

[0078] The desired compound (Compound C) is obtained in a manner similar to that of Example 1 except that tetrahydrofuran-3-carboxylic acid is used instead of (S)-tetrahydrofuran-2-carboxylic acid in Example 1.
M. p.: 179-180°C (recrystallized from ethyl acetate)

Preparation 1: Preparation of tablets	
(S)-4-amino-5-chloro-2-methoxy-N-[-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide · fumarate (Compound 2)	5 g
Lactose	80 g
Corn starch	30 g
Crystalline cellulose	25 g
Hydroxypropyl cellulose	3 g

[0079] The above components are mixed and granulated in a conventional manner, and thereto are added light anhydrous silicic acid (0.7 g) and magnesium stearate (1.3 g). The mixture is further tabletted to give 1,000 tablets (each 145 mg).

Preparation 2: Preparation of capsules	
(S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide · fumarate (Compound 2)	5 g
Lactose	165 g
Corn starch	22 g
Hydroxypropyl cellulose	3.5 g
Light silicic acid	1.8 g
Magnesium stearate	2.7 g

[0080] The above components are mixed and granulated in a conventional manner, and the mixture is packed into a capsule to give 1,000 capsules.

Preparation 3: Preparation of powder	
(S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide · fumarate (Compound 2)	10 g
Lactose	960 g
Hydroxypropyl cellulose	25 g
Light silicic acid	5 g

[0081] The above components are mixed by a conventional manner to give a powder preparation.

Preparation 4: Preparation of injection (amount for 1000 ampoules)	
(S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl] benzamide · fumarate (Compound 2)	2 g
Sorbitol	100 g
Distilled water for injection	q.s.
Total	2000 ml

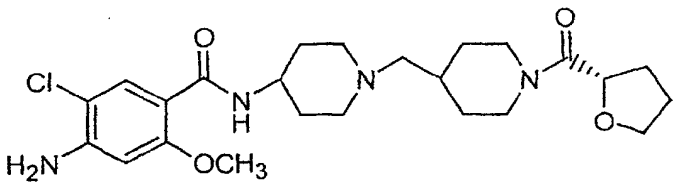
[0082] (S)-4-Amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide fumarate (Compound 2) and sorbitol are dissolved in a portion of distilled water for injection, and thereto is added a remaining portion of distilled water for injection to adjust the total volume of the mixture. The solution thus obtained is filtered through a membrane filter (0.22 μm), and each 2 ml of the filtrate is filled into ampoules, which are further sterilized at 121°C for 20 minutes.

INDUSTRIAL APPLICABILITY

[0083] The compound (I) of the present invention and a pharmaceutically acceptable acid addition salt thereof show not only a potent affinity for 5-HT_4 receptor and a potent enhancing activity of defecation, but show quite weak side effects, for example, no antagonistic activity on dopamine D_2 receptor and few effects on the heart, and hence, they can be useful in the prophylaxis or treatment of various diseases such as gastrointestinal diseases (e.g., irritable bowel syndrome, flaccid constipation, habitual constipation, drug-induced constipation (e.g., constipation induced by morphine or a psychotropic) central nervous diseases (e.g., schizophrenia, depression, disturbance of memory or anxiety), and urinary diseases (e.g., urinary disturbances such as dysuria accompanied by urinary obstruction or prostatomegaly), or various gastrointestinal dysfunctions (e.g., anorexia, nausea, vomiting or abdominal fullness) accompanied by the treatment of various diseases as mentioned above. Therefore, they are useful especially as a gastrointestinal motility enhancer or a gastrointestinal prokinetic agent. In addition, the compound of the formula (III) is useful as an intermediate for preparing the compound of the formula (I).

Claims

1. An (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl)benzamide of the following formula (I):



(I)

or a pharmaceutically acceptable acid addition salt thereof, or a hydrate thereof.

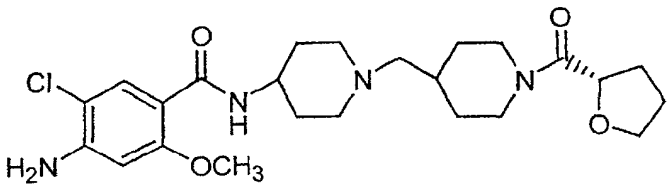
2. An (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide according to claim 1 or a hydrate thereof.

3. An (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide fumarate according to claim 1 or a hydrate thereof.

4. An (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide maleate according to claim 1 or a hydrate thereof.

5. A pharmaceutical composition, which comprises as an active ingredient an (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide, or a pharmaceutically acceptable acid addition salt thereof, or a hydrate thereof in admixture with a conventional pharmaceutically acceptable carrier or diluent.

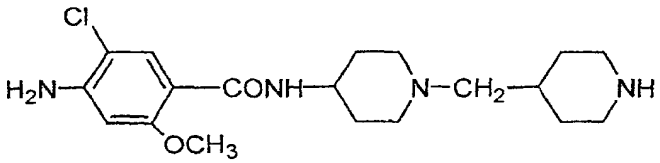
6. A process for preparing an (S)-4-amino-5-chloro-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamide of the following formula (I):



(I)

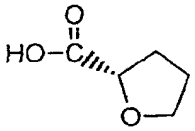
or a pharmaceutically acceptable acid addition salt thereof, which comprises the following process (a) or (b):

(a) reacting a compound of the formula (II):



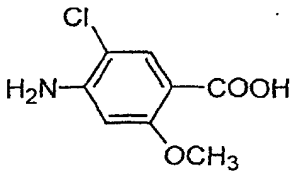
(II)

with a compound of the formula (III):



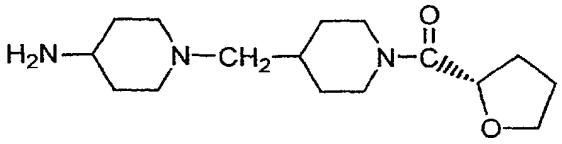
(III)

(Chemical name: (S)-tetrahydrofuran-2-carboxylic acid) or a reactive derivative thereof, or
(b) reacting a compound of the formula (IV):



(IV)

or a reactive derivative thereof, with a compound of the formula (V):



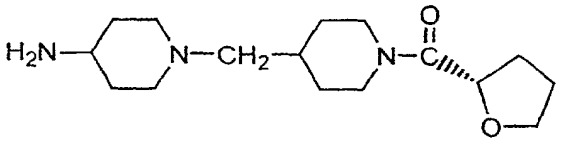
(V)

and if necessary, followed by converting the product into a pharmaceutically acceptable acid addition salt thereof.

7. Use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable acid addition salt thereof, in the preparation of a medicament for the treatment of diseases caused by the lack of stimulation on serotonin 4-receptor.

8. Use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable acid addition salt thereof, in the preparation of a medicament for the treatment of gastrointestinal motility disorders or gastrointestinal dysfunction.

9. An (S)-4-amino-1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]piperidine of the following formula (V):



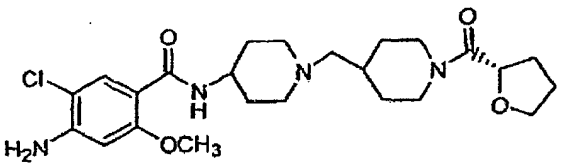
(V)

or an acid addition salt thereof.

10. A compound according to any one of claims 1 to 4 for use as a pharmaceutical.

Patentansprüche

1. (S)-4-Amino-5-chlor-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamid der folgenden Formel (I):



(I)

oder ein pharmazeutisch annehmbares Säureadditionssalz davon oder ein Hydrat davon.

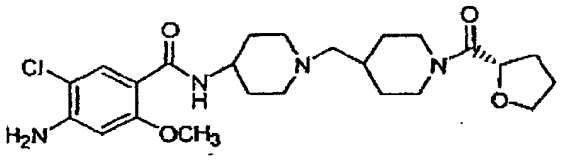
2. (S)-4-Amino-5-chlor-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamid gemäß Anspruch 1 oder ein Hydrat davon.

3. (S)-4-Amino-5-chlor-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamid Fumarat nach Anspruch 1 oder ein Hydrat davon.

4. (S)-4-Amino-5-chlor-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamid Maleat nach Anspruch 1 oder ein Hydrat davon.

5. Pharmazeutische Zusammensetzung, die als aktives Ingredienz (S)-4-Amino-5-chlor-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamid oder ein pharmazeutisch annehmbares Säureadditionssalz davon oder ein Hydrat davon im Gemisch mit einem herkömmlichen pharmazeutisch annehmbaren Träger oder Verdünnungsmittel umfasst.

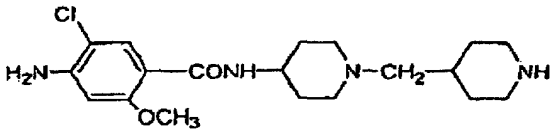
6. Verfahren zur Herstellung von S)-4-Amino-5-chlor-2-methoxy-N-[1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]-4-piperidinyl]benzamid der folgenden Formel (I):



(I)

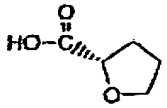
oder eines pharmazeutisch annehmbaren Säureadditionssalzes davon, dass das folgende Verfahren (a) oder (b) umfasst:

(a) Umsetzen einer Verbindung der Formel (II):



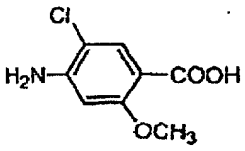
(II)

mit einer Verbindung der Formel (III) :



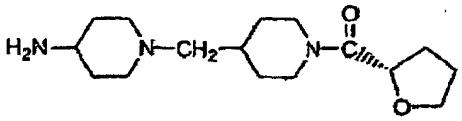
(III)

(Chemischer Name: (S)-Tetrahydrofuran-2-carbonsäure) oder einem reaktiven Derivat davon, oder
(b) Umsetzen einer Verbindung der Formel (IV):



(IV)

oder eines reaktiven Derivats davon mit einer Verbindung der Formel (V) :



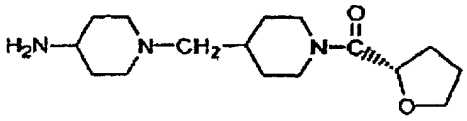
(V)

und, wenn notwendig, anschließende Umwandlung des Produkts in ein pharmazeutisch annehmbares Säureadditionssalz davon.

7. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 4 oder eines pharmazeutisch annehmbaren Säureadditionssalzes davon bei der Herstellung eines Medikaments zur Behandlung von Krankheiten, die durch Fehlen einer Stimulation auf den Serotonin-4-Rezeptor verursacht werden.

8. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 4 oder eines pharmazeutisch annehmbaren Additionssalzes davon bei der Herstellung eines Medikaments für die Behandlung gastrointestinaler Motilitätsstörungen oder gastrointestinaler Dysfunktion.

9. (S)-4-Amino-1-[1-(2-tetrahydrofurylcarbonyl)-4-piperidinylmethyl]piperidin der folgenden Formel (V):



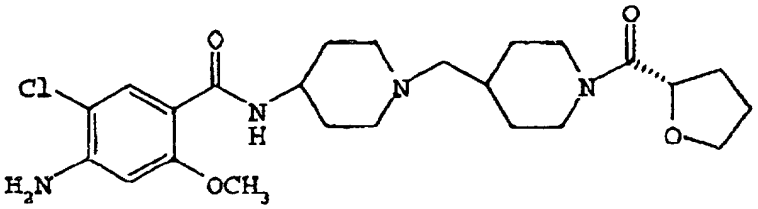
(V)

oder ein Säureadditionssalz davon.

10. Verbindung nach einem der Ansprüche 1 bis 4 zur Verwendung als Pharmakon.

Revendications

1. (S)-4-amino-5-chloro-2 méthoxy-N-[1-[1-(2-tétrahydrofurylcarbonyl)-4-pipéridinylméthyl]-4-pipéridinyl]benzamide de formule (I) qui suit :



(I)

ou l'un de ses sels d'addition d'acide pharmaceutiquement acceptables, ou l'un des hydrates.

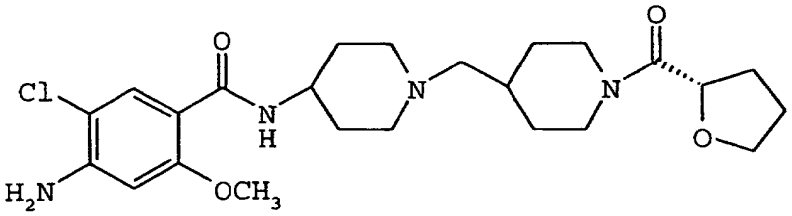
2. (S)-4-amino-5-chloro-2-méthoxy-N-[1-[1-(2-tétrahydrofurylcarbonyl)-4-pipéridinylméthyl]-4-pipéridinyl]benzamide selon la revendication 1 ou l'un de ses hydrates.

3. Fumarate de (S)-4-amino-5-chloro-2-méthoxy-N-[1-[1-(2-tétrahydrofurylcarbonyl)-4-pipéridinylméthyl]-4-pipéridinyl]benzamide selon la revendication 1 ou l'un de ses hydrates.

4. Maléate de (S)-4-amino-5-chloro-2-méthoxy-N-[1-[1-(2-tétrahydrofurylcarbonyl)-4-pipéridinylméthyl]-4-pipéridinyl]benzamide selon la revendication 1 ou l'un de ses hydrates.

5. Composition pharmaceutique comprenant en tant qu'ingrédient actif le (S)-4-amino-5-chloro-2-métoxy-N-[1-[1-(2-tétrahydrofurylcarbonyl)-4-pipéridinylméthyl]-4-pipéridinyl]benzamide, ou l'un de ses sels d'addition d'acide pharmaceutiquement acceptables, ou l'un des hydrates, en association avec un véhicule ou diluant usuel pharmaceutiquement acceptable.

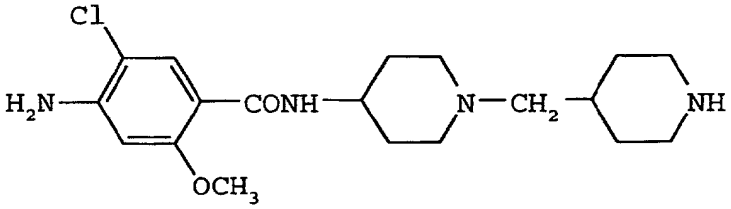
6. Procédé pour préparer le (S)-4-amino-5-chloro-2-méthoxy-N-[1-[1-(2-tétrahydrofurylcarbonyl-4-pipéridinylméthyl]-4-pipéridinyl]benzamide de formule (I) ci-après :



(I)

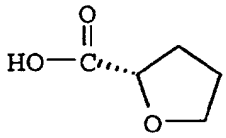
ou l'un de ses sels d'addition d'acide pharmaceutiquement acceptables, ou l'un des hydrates, ledit procédé comprenant le processus (a) ou (b) ci-après:

(a) réaction d'un composé de formule (II) :



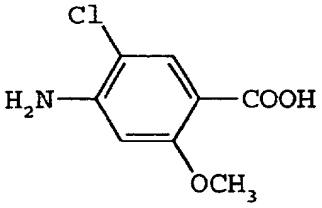
(II)

avec un composé de formule (III) :



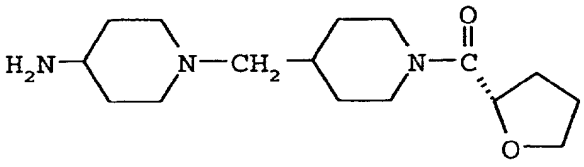
(III)

(nomenclature chimique : acide (S)-tétrahydrofurane-2-carboxylique) ou l'un de ses dérivés réactifs, ou
(b) réaction d'un composé de formule (IV) :



(IV)

ou l'un de ses dérivés réactifs, avec un composé de formule (V) :



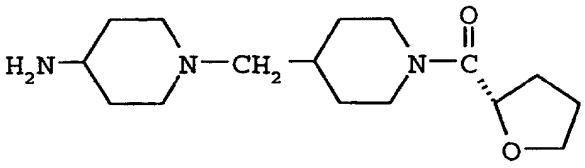
(V)

et ensuite, si nécessaire, conversion du produit en l'un de ses sels d'addition d'acide pharmaceutiquement acceptables.

7. Utilisation d'un composé selon l'une quelconque des revendications 1 à 4, ou de l'un de ses sels d'addition d'acide pharmaceutiquement acceptables, dans la préparation d'un médicament pour le traitement de maladies provoquées par un défaut de stimulation du récepteur 4 de la sérotonine.

8. Utilisation d'un composé selon l'une quelconque des revendications 1 à 4, ou de l'un de ses sels d'addition d'acide pharmaceutiquement acceptables, dans la préparation d'un médicament pour le traitement de désordres de la motilité gastro-intestinale ou de dysfonction gastro-intestinale.

9. (S)-4-amino-1-[1-(2-tétrahydrofurylcarbonyl)-4-pipéridinylméthyl]pipéridine de formule (V) :



(V)

ou l'un de ses sels d'addition d'acide.

10. Composé selon l'une quelconque des revendications 1 à 4 pour utilisation en tant produit pharmaceutique.